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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/620,820	07/21/2000	Alan D. Attie	960296.97290	4397

7590 05/17/2005

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/620,820	ATTIE ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are pending in the application. Claims 13-16 are withdrawn from consideration for being directed non-elected subject matter. Claims 1-12 and 17 are currently under examination.

This Office Action is in response to the Amendment filed on 2/4/05.

Response to Amendment

The rejection of claims 1-12 and 17 under 35 U.S.C.103 (a) is maintained for reasons set forth of the record mailed on 7/28/04 and further discussed below.

Response to Arguments

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-12 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Twisk et al., in view of Teasdale and Jackson and Attie et al.

In response to this rejection, Applicants argue that the success of the method and product as taught by this application was not predictable from the cited prior art because there is not a reasonable expectation of success. Applicants assert that there were multiple uncertainties in practice the claimed method, wherein the prior art does not demonstrate that this result could actually be achieved. Applicants assert Teasdale and Jackson reference teaches that it is unclear whether all proteins can be retained in ER by KDEL or other signals tagged for ER. Applicants further assert this reference teaches that chimeric molecules tagged with KDEL are often modified by the golgi enzymes, wherein the endogenous protein having such signal peptides are

not modified in this way. Applicants thus reasoned that since the molecule recited in the claim is a non-native protein, it is unpredictable whether it would be modified by the golgi apparatus of the cell. Applicants further argue that the complete success and functionality of the molecule cannot be predicted in advance when an additional domain is added because the protein is a highly complex three-dimensional structure. Applicants assert that it was not clear whether the fusion created by the LDLR 354 protein and KDEL signal peptide would be aggregated in the ER and be sequester in a form in which the binding site for the receptor would be available for binding to apoE in that reticulum. Applicants argue that it is not clear whether the attachment would leave the soluble receptor in a form and orientation so that binding to apoE would still occur even though Teasdale and Jackson paper suggest some proteins with the signal would attach to the ER. Furthermore, Applicants assert that it is unclear whether the ER is the right place in the secretion pathway in which to trap apoB. Applicants also assert that it is unclear whether the receptors would be overwhelmed or presented in sufficient amount or if other mechanisms would permit apoB secretion when the truncated receptors were expressed in mammalian cells. Moreover, Applicants assert that it is unclear that the soluble LDL receptor would still function if trapped in the ER to bind and destroy apoB. Lastly, Applicants argue that it is unclear whether the expression cassette can be expressed in animals to result in meaningful levels of protein and achieve sequestration of apoB and prevent its secretion in measurable amount. Applicants thus conclude the claimed method is not obvious in view of the cited art.

The above arguments have been fully considered but deemed unpersuasive. The teachings of the prior art and reasons for obviousness were discussed in detail in the office action mailed on 7/28/04. In response to Applicants' argument with regard to whether the chimeric

receptor would be retained in ER, the examiner maintains the position that Teasdale and Jackson provides reasonable expectation of success that the chimeric protein with ER retaining signal peptide would be retained in the ER. This reference not only teaches signal peptides that are capable of retaining the peptide in ER (see table 1) but also the well established mechanism of K/HDEL retaining is due to retrieval of the protein from post ER compartment (see page 36, last paragraph through page 37, 1st paragraph). Whether the chimeric protein would be modified by the golgi enzymes is irrelevant to the outcome of the claimed method because the native LDL receptor would also go through golgi for post translational modification before it is directed to cell membrane. With regard to Applicants' argument of unpredictability of the functionality of the chimeric protein, the combined teaching of Twisk, Teasdale and Jackson and Attie et al. provides sufficient teaching that such chimeric protein would be functional for binding apoB, whereas binding of apoE is not necessary for the success of this method. As discussed above, Teasdale and Jackson teaches that mechanism of the ER retaining capability of the signal peptide, it does not appear to affect the function of the protein that it attaches to. None of the examples given in the reference shows altered functionality. Moreover, other prior art references also demonstrate that attaching an ER retention signal peptide to a given peptide does not affect its function when localized in ER. For example, Chiba et al. (1998, JBC, vol. 273, no. 41, pages 26298-26304) demonstrated that a glycosylation enzyme attached with HDEL signal peptide localized in ER and retains its activity (see abstract and page 26300, 2nd col., result section through page 26301, 1st col.). Thus, absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to expect the LDLR354 attached with

HDEL or other ER signal peptide would leave the receptor in a form and orientation that binding of apoB still occurs.

With regard to Applicants argument that it is unclear whether the ER is the right place in the secretion pathway in which to trap apoB before the work described in the instant application, the examiner simply cannot agree with this point. Applicants' attention is directed to Twisk et al., especially page 530, Figure 7, and 1st paragraph of 1st column, wherein it clearly states that apoB degradation occurs in ER by either LDLR dependent or independent manner. As an overall process of LDL synthesis and degradation pathway, even other forms of apoB secretion is present, the LDLR dependent degradation of apoB increases because of the retention of apoB bound LDLR in ER. Thus, the overall level of secretion would be decreased, thus decreases the synthesis of LDL. Attie et al. demonstrated that soluble LDLR354 is able to bind LDL, an ordinary artisan would have reasonable expectation of success to attach a ER retention signal peptide to it, wherein the said receptor can still bind LDL molecule. None of the protein loses its function when it is attached with the signal peptide as disclosed in Teasdale and Jackson. Further, as disclosed by Chiba, the glycosylation enzyme also functions normally when it is attached with the HDEL signal peptide. Absent evidence from contrary, one of ordinary skill in the art would have reasonable expectation of success in make and practice the invention based on the teaching of the prior art.

Lastly, in response to Applicants' argument with regard to uncertainty arise from genetic engineering of whether the protein can be expressed in level that sufficient to sequester apoB, Applicants' attention is specifically directed to the teaching of Twisk, page 526, 2nd col., 3rd paragraph through page 527, 1st col. Twisk teaches that adenovirus-mediated overexpression of

LDL receptor not only able to express in hepatocytes but also in a level that restores degradation of apoB in hepatocytes in a measurable level. Thus, absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success that adenoviral transfer of the expression cassette encoding the truncated LDL receptor attached with a ER retaining signal peptide can be expressed in sufficient level to enhance apoB degradation thus reduce LDL synthesis and serum cholesterol level. Therefore, for reasons discussed in the previous office actions and above, the claimed invention is obvious in view of the cited art. This rejection is thus maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

This application contains claims 13-16 drawn to an invention nonelected with traverse in the response filed on 6/14/02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELIAN QIAN
PATENT EXAMINER